Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus

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Abstract: The use of different definitions for bronchopulmonary dysplasia (BPD) has been an ongoing challenge. We searched papers published in English from 2010 and 2015 reporting BPD as an outcome, together with studies that compared BPD definitions between 1978 and 2015. We found that the incidence of BPD ranged from 6% to 57%, depending on the definition chosen, and that studies that investigated correlations with long-term pulmonary and/or neurosensory outcomes reported moderate-to-low predictive values regardless of the BPD criteria. CONCLUSION A comprehensive and evidence-based definition for BPD needs to be developed for benchmarking and prognostic use.

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Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus

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Short Title: Bronchopulmonary dysplasia definitions in neonates

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ABSTRACT

The use of different definitions for bronchopulmonary dysplasia (BPD) has been an on-going challenge. We searched papers published in English from 2010 and 2015 reporting BPD as an outcome, together with studies that compared BPD definitions between 1978 and 2015. We found that the incidence of BPD ranged from 6% to 57%, depending on the definition chosen, and that studies that investigated correlations with long-term pulmonary and, or, neurosensory outcomes reported moderate to low predictive values regardless of the BPD criteria. **Conclusion.** A comprehensive and evidence-based definition for BPD needs to be developed for benchmarking and prognostic use.

Key Words: Bronchopulmonary dysplasia, Chronic lung disease, Pulmonary insufficiency, National Institute of Child Health and Human Development, Quality improvement

Key Notes

- The use of different definitions for bronchopulmonary dysplasia (BPD) has been an ongoing challenge.
- We found that the incidence of BPD ranged from 6% to 57%, depending on the definition chosen, and studies investigating correlations with long-term pulmonary and, or, neurosensory outcomes reported moderate to low predictive values regardless of the BPD criteria.
- A comprehensive evidence-based definition for BPD needs to be developed for benchmarking and prognostic use.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common morbidity of surviving preterm infants and is associated with adverse long-term pulmonary and neurodevelopmental outcomes (1). With advances in perinatal care increasing the survival of extremely preterm infants, the incidence of BPD has either remained static or risen in the last 20 years (2,3). Given that BPD rates vary depending upon the centre, country and population examined, comparisons of its prevalence between studies remains a challenge. A major factor contributing to the variation in reported BPD rates is the definitions used to classify the condition in neonates. In 2012, a comparative study reported significant variabilities in the definitions used to classify outcomes in international data (2), including BPD. The use of different definitions hampers comparisons or the ability to synthesise the results of drugs trials and other interventions in neonatal practice. These drawbacks highlight the need for efforts to harmonise definitions and establish a unified system of classification for BPD diagnosis (4,5).

Since its initial identification in 1967 by Northway et al (6), the criteria and definitions used to diagnose BPD have undergone a number of modifications. A number of different criteria for BPD have appeared in the literature since then, beginning with definitions developed for chronic lung disease (CLD) by Tooley (7) in the late 1970s, to modifications made by Shennan et al (8) in the late 1980s (7-11). By the early 1990s, the Neonatal Research Network of the American National Institute of Child Health and Human Development (NICHD) raised concerns over the wide variation in BPD incidence rates reported across its sites. These challenges were later addressed at an NICHD workshop in 2001, resulting in the proposal for a consensus definition for BPD (12). Despite these efforts, variations in definitions used in contemporary BPD clinical research studies to describe BPD as a main outcome still exist and are highlighted in Table 1. Therefore, our primary objective was to conduct a scoping review of different BPD definitions used in peer-reviewed publications between 2010 and 2015 and to determine the variations in definitions used in

published studies. Our secondary objective was to review studies that compared different definitions of BPD in the same cohort with the explicit intention of comparing definitions and to review studies where such comparisons were extended to long-term neonatal respiratory and, or, neurodevelopmental outcomes.

METHODS

Study selection

We included human-based studies that listed BPD, CLD or prematurity-related respiratory insufficiency as either a primary or a secondary outcome. This encompassed randomised controlled studies, retrospective and prospective cohort studies, case-control studies, case-series, pre-post design, cross-sectional and questionnaire design studies. We excluded survey design studies using unclear definitions to describe BPD in participants, as well as animal and *in vitro* studies. We also excluded studies that evaluated the diaphragmatic hernia population, as it is a special condition-related situation. Studies that were only reported as protocols were also excluded from our analysis.

For the secondary objective, we included studies that used two or more definitions of BPD in the same population, with the explicit purpose of comparing definitions. We also collected information on incidences or correlation or diagnostic statistics related to either long-term respiratory or neurodevelopmental outcomes in infancy or childhood, if available.

Search strategy

With the help of an experienced librarian, we searched the PubMed database to identify eligible studies for both objectives. For the primary objective, the search was confined to studies published between 2010 and 2015. For the secondary objective, we included studies published between 1978 and 2015, in order to capture all the eligible studies that compared at least two definitions of BPD and their respective predictive ability

for adverse long-term outcomes. For both objectives, the studies were limited to those published in English. The detailed search strategy and identified literature is reported in Appendix 1.

Data collection

All eligible studies identified from the initial search underwent title and abstract screening by one reviewer (DH), followed by a full-text review of potentially relevant articles by two reviewers (DH and PS). Any differences noted between the two reviewers were resolved by consensus. After a full-text review, data were extracted from all selected studies, including: the year of publication, country of origin, whether it was a single or multicentre study), whether a definition of BPD was listed, whether BPD was a primary outcome, the type of definition - namely a physiological criteria-based definition or a definition that included death - and the categorisation of severity of BPD. Studies that compared various definitions of BPD were reviewed separately and information on the rates of BPD diagnosis, and its correlation with respiratory or neurodevelopmental outcomes, were extracted.

The review protocol was registered on the International prospective register of systematic reviews (PROSPERO), with the registration number CRD42016035931. PROSPERO aims to provide a comprehensive listing of systematic reviews registered at inception to help avoid duplication and allow researchers to comply with the Preferred Reporting Items for Systematic Reviews and Meta-analyses.

RESULTS

The detailed search results are reported in Figure 1. Of the initial 2,134 papers we identified, 820 were included in our review. Of these, 628 (77%) reported a definition for BPD, whereas 192 (23%) failed to provide a definition despite reporting BPD as an outcome.

A comparison of the baseline characteristics of the studies that defined BPD versus those that failed to provide a definition is outlined in Table 2. There were no differences

between studies reporting a definition or not with regards to the continent of the study, whether it was a single or multicentre study and the year of publication. The definition was more likely to be clearly documented in case series and case control and cross-sectional studies than in clinical trials or cohort studies. Of the studies in which BPD was chosen as the primary outcome, 17% did not define the criteria used.

Table 3 describes various characteristics of the studies that defined BPD. Overall, 45% of papers reported the Shennan et al (8) definition, whereas 30% used the NICHD consensus definition (12). The use of a physiological definition such as an oxygen challenge test (11) was reported in approximately 6% of the papers reviewed. Only 5% of the studies contained information on whether neonates who died before meeting the criteria for BPD cut-offs – such as 28 days of age or 36 weeks post menstrual age - were included in the denominator. The severity of BPD was defined in 30% of the reports and of these, BPD was classified as mild, moderate or severe in 132 studies (70%), as moderate or severe in 28 (15%), as severe in only 18 (10%) and as mild or moderate in one study (<1%). Different types of classifications were used in eight (4%) of the studies and one study categorised the severity without providing a description.

The findings of the secondary objectives are reported in Tables 4 and 5. There were 11 studies that explicitly compared at least two definitions of BPD in the same cohort of neonates and, of these, five reported on the correlations between definitions and infantile or childhood respiratory or neurodevelopmental outcomes. Marked variations in the rate of BPD were identified depending upon the definition and denominator population used, including just the neonates who survived, all the eligible neonates in the studies, irrespective of early death and just the eligible neonates that there was data for. Overall, the rates of BPD were higher when Tooley (7) or Bancalari et al (9,13) definitions were applied, than when the Shennan et al definition was used (8). Furthermore, a comparison of the Shennan et al (8) and the NICHD consensus definitions (12) also demonstrated variable rates based upon the

denominator population. However, the differences between the definitions in predicting long-term outcomes were minimal.

DISCUSSION

In the five decades since it was first described, the definition or characterisation of BPD has undergone several iterations (6,9,12,14-16). This scoping review presents these various modifications and forms of BPD definitions, in addition to their frequency of use in publications. Our review confirms that published reports are still highly variable in terms of BPD definitions. Approximately, one-quarter of the papers did not define BPD despite the inclusion of morbidity as an outcome in their studies. Meanwhile, a significant relationship was noted between study types and whether a definition for BPD was reported or not. Approximately half of the reports that defined BPD used the definition outlined by Shennan et al (8), whereas one-third of the reports either used the NICHD definition or its modified version (12). The proposed physiologic definition, such as an oxygen challenge test (11), was used in a very small number of reports with marked variability. In the majority of studies, it was unclear how the denominator was selected to calculate BPD incidence with respect to death or discharges occurring before the specified cut-off criteria. Moreover, marked differences in the rate of BPD were observed in the same study cohort when different prepositions within the definitions were used, such as *at* or *for* or *on*. For example, the NICHD (12) criteria are ambiguous and the original specification regarding receipt of oxygen *for* 28 days has since been misinterpreted as receiving oxygen *at* 28 days in many reports. Comparisons of BPD definitions revealed that these definitions had low to moderate predictive values in terms of abnormal pulmonary or neurological outcomes in early childhood.

To our knowledge, our review was the first to assess the variability of BPD definitions reported in all types of peer-reviewed publications. The major strengths of this scoping review included the comprehensive selection of studies published in the last six years, the large number of studies included and the attempt to identify nuances associated with

different nomenclatures of BPD. This review permitted the extraction of data from a wide selection of study designs, while allowing the narrative integration of the relevant evidence. We intended to keep this as a scoping review as our purpose was to be more exploratory in addressing the question of *what* rather than *how*. We neither assessed the quality of the included studies nor collected data on the rate of BPD from each study, because the baseline population varied too much between studies to draw any meaningful conclusions. Another limitation of this review was the selection of only English language studies from one database, as it would not have been practically feasible to cover many languages and databases on this topic.

A systematic review of randomised controlled trials of agents for preventing BPD that was published between 1992 and 2014 reported that the definition described by Shennan et al (8) was the most commonly used, in 71% of trials, followed by that of Bancalari et al (9) in 45% of trials. Interestingly, some trials reported rates using multiple definitions (17). However, this review was limited to clinical trials, as variations in other types of studies were not explored. The issue of non-comparable BPD definitions has surfaced since the liberal use of non-invasive support and the recognition of oxygen-induced and atelectasis-associated injury in immature lungs. In order to keep alveoli adequately expanded, and to avoid oxygen-related lung injury, many neonates are now managed on higher end expiratory pressure (10) provided via non-invasive respiratory support. This leads to the reduced use of oxygen, at the cost of high end-expiratory pressure. Because they are in room air, these infants do not meet the traditional cut-off of the need for oxygen at a specified time. This feature defeats the underlying basis for the definition of BPD, which originally aimed to identify neonates who had chronic pulmonary insufficiency and were not able to fully support their own respiration without assisted support and faced a higher risk of abnormal pulmonary and, or, respiratory outcomes (6,9). The NICHD (12) definition addresses this issue by classifying neonates that require any positive pressure support at 36 weeks of postmenstrual age as having moderate or severe BPD. However, this introduces other uncertainties, especially with regard to neonates who are receiving humidified high-flow air via a nasal

cannula. In Canada, it was shown that by applying the Shennan et al definition (8), approximately 10% of neonates of less than 33 weeks of gestation were excluded from having pulmonary insufficiency at 36 weeks, because they were receiving positive pressure support but were in room air (18). The Shennan et al (8) definition also has inherent limitations regarding applicability, as another study showed that several neonates were transferred to step-down units or discharged home before 36 weeks and, therefore, may not have been included in the data or may have had imputed data. The inclusion or exclusion of neonates discharged before 36 weeks in the denominator can lead to over- or under-reporting of BPD rates (19). Meanwhile, the criteria proposed by the NICHD (12) are ambiguous in that the original specification regarding receipt of oxygen *for* 28 days has since been misinterpreted as receiving oxygen *at* 28 days in many reports. This subtle change in semantics can influence the rate of BPD dramatically (13). For instance, Bancalari and Claure (13) reported that being on oxygen *for all* of the first 28 days classified only 6% of neonates as having BPD, whereas oxygen *at* 28 days categorised 57% of neonates with the condition. In addition, the NICHD definition classifies all neonates as having BPD if they are on oxygen *at or for* 28 days. Apart from the additional advantage of classifying neonates as mild, moderate and severe categories, this definition is similar to the definition proposed by Bancalari (9) in the late 1970s. Thus, it appears that no single definition or criteria used for to diagnose BPD is ideal. Our review also raises an important point about whether dichotomising BPD at a set cut-off is an appropriate measure or whether the richness of continuous data, such as the duration of respiratory support or duration of oxygen therapy prior to discharge home, is a better alternative for predicting long-term respiratory and neurodevelopmental health. This needs to be addressed in future studies.

Another important finding of this review was the correlation between definitions and pulmonary or neurodevelopmental outcomes during infancy or childhood. Our analysis revealed marked differences in the childhood outcomes assessed. It varied from simple, yet highly unreliable measures of the use of bronchodilator to neonatal death prior to assessment. This underlines the importance of identifying outcomes that are patient-centred

and those that affect the quality of life for a child and their caregivers. In addition, none of the definitions or cut-offs were significant enough for clinical use.

The bigger overarching question is how to proceed from here? As a global neonatal and perinatal community, we need to achieve a consensus on: (a) the need to identify or label a child with a chronic condition, (b) the aim of defining, predicting or identifying chronic pulmonary insufficiency of prematurity, (c) the outcomes to be predicted based on certain postnatal criteria and (d) the individuals who will determine these predictors and outcomes, such as practitioners, other healthcare workers and, or, the parents, as stakeholders. Ultimately, the least concern that parents have is whether their child required oxygen at 35 weeks or 37 weeks. Instead, parents would prefer to see their child healthy, with no residual pulmonary and neurodevelopmental consequences of preterm birth. From a practitioner and policymaker perspective, it is important to identify children who will require increased use of long-term resources, so that preventative secondary and tertiary measures can be implemented before a child is discharged from the neonatal unit. Meanwhile, healthcare workers would prefer to have interim indicators that they can strive to achieve using different clinical care and quality improvement strategies that are measurable, achievable and reproducible. Thus, when it comes to pulmonary insufficiency of prematurity it is essential to strike a balance between the need for prediction from the policy-makers' and planners' perspectives, the need for easy interim criterion development from the practitioners' perspective and the need for meaningful outcome detection from the parents' and practitioners' perspectives associated with. To accomplish this, further efforts should focus on the discovery and development of biomarkers for the prediction of future respiratory and neurodevelopmental outcomes of preterm neonates. However, until these biomarkers are identified we have to use the existing available clinical information in such a way that an informative perspective can be gained by considering respiratory status in the interim period prior to discharge home. A clearer objective definition of BPD will also provide an opportunity for successful preventative and treatment strategies, including potential drug development (17).

CONCLUSION

Our review identified marked differences in the use of various definitions for BPD across a spectrum of different clinical research study designs. In order to inform and establish a consistent definition of BPD in peer-reviewed literature, it is essential to develop criteria, by consensus, using data-driven approaches and engaging key stakeholders, parents and families. From a research perspective, further evaluation of the prospective and retrospective data on childhood respiratory and, or, neurodevelopmental outcomes is needed to validate, refute and suggest new cut-offs that incorporate current and contemporary respiratory support practices.

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Abbreviations:

BPD, Bronchopulmonary dysplasia; CLD, Chronic lung disease; NICHD, National Institute of Child Health and Human Development;

Conflict of Interest: The authors have no conflicts of interest to declare.

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Figure Legends:

Figure 1: Flow chart of Bronchopulmonary Dysplasia (BPD) study selection

Box 1: Definitions of Bronchopulmonary Dysplasia in Preterm Infants: Review Search Strategy

Search strategy	Results
Infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, premature/ or infant, extremely premature/ or (low adj3 gestational age).ti,ab. Or (small adj3 gestational age).ti,ab. Or neonat*.ti,ab. Or premature*.ti,ab. or preterm.ti,ab. or low birth weight.ti,ab. or (VLBW or ELBW).ti,ab. AND Chronic lung disease.ti,ab. or bronchopulmonary dysplasia/ or bronchopulmonary dysplasia.ti,ab. or oxygen inhalation therapy/ut [utilization] or continuous positive airway pressure/ or (CPAP or continuous positive airway pressure).ti,ab. Not: exp animal/ not human/ Not: limit to (case reports or comment or editorial or historical article or letter) Limit to (yr=2010-current and English)	2133
Infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, premature/ or infant, extremely premature/ or (low adj3 gestational age).ti,ab. Or (small adj3 gestational age).ti,ab. Or neonat*.ti,ab. Or premature*.ti,ab. or preterm.ti,ab. or low birth weight.ti,ab. or (VLBW or ELBW).ti,ab. AND respiratory insufficiency/ or respiratory insufficiency.ti,ab. Not: exp animal/ not human/ Not: limit to (case reports or comment or editorial or historical article or letter) Limit to (yr=2010-current and English)	245
Infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, premature/ or infant, extremely premature/ or (low adj3 gestational age).ti,ab. Or (small adj3 gestational age).ti,ab. Or neonat*.ti,ab. Or premature*.ti,ab. or preterm.ti,ab. or low birth weight.ti,ab. or (VLBW or ELBW).ti,ab. AND respiratory distress syndrome, newborn/ Not: exp animal/ not human/ Not: limit to (case reports or comment or editorial or historical article or letter) Limit to (yr=2010-current and English)	505

Table 1: Various definitions of BPD identified in literature

Reference	Definition	
Northway, 1967(6)	Prolongation of the healing phase of respiratory-distress syndrome combined with a generalized pulmonary oxygen toxicity involving mucosal, alveolar and vascular tissues.	
Tooley, 1979(7)	At 30 days of postnatal age, an infant who has any radiologic abnormality of the lung parenchyma plus at least of one the following: (1) an oxygen tension in arterial blood breathing air of 60 mm of Hg (7.99 kPa) or less, (2) carbon dioxide tension in arterial blood of more than 45 mm of Hg (5.99 kPa), and /or (3) oxygen dependence (i.e. requires an FiO_2 of more than 0.21).	
Bancalari, 1979(9)	An infant who has: (1) required intermittent positive pressure ventilation during the first week of life and for a minimum of three days, (2) developed clinical signs of chronic respiratory disease characterized by tachypnea, intercostal and subcostal retraction, and rales on auscultation, all persisting for longer than 28 days, (3) required supplemental oxygen for more than 28 days to maintain a PaO_2 over 50 mm Hg, and (4) chest radiograph showed persistent strands of densities in both lungs, alternating with areas of normal or increased lucency.	
Shennan,1988(8)	Requirement for additional oxygen at 36 weeks post-menstrual age (PMA) in infants born with a birth weight of less than 1,500 g.	
National Institute of Child Health and Human Development (NICHD) 2001(12)	Gestational age <32 weeks	Gestational age ≥ 32 weeks
	Time point of assessment: 36 weeks PMA or discharge to home, whichever comes first	Time point of assessment: >28 d but <56 d postnatal age or discharge to home, whichever comes first
	Treatment with oxygen > 21% for at least 28 days and:	
	Mild BPD: Breathing room air at 36 weeks PMA or discharge, whichever comes first Moderate BPD: Need for <30% oxygen at 36 weeks PMA or discharge, whichever comes first Severe BPD: Need for ≥ 30% oxygen and/or positive pressure, (positive pressure ventilation or NCPAP) at 36 weeks PMA or discharge, whichever comes first.	Mild BPD: Breathing room air at 56 days postnatal age or discharge, whichever comes first Moderate BPD: Need for <30% oxygen at 56 days postnatal age or discharge, whichever comes first Severe BPD: Need for ≥ 30% oxygen and/or positive pressure, (positive pressure ventilation or NCPAP) at 56 days postnatal age or discharge, whichever comes first.
Walsh, 2004(16)	Same as NICHD definition, but infants in supplemental oxygen <0.30 underwent an oxygen challenge test with timed stepwise reduction to room air. Those who failed the reduction test were diagnosed with BPD.	
Vermont Oxford Network(20)	Infants who required supplemental oxygen at 36 weeks PMA. Infants who went home requiring supplemental oxygen at 34 to 36 weeks PMA were classified as having BPD. For infants who were discharged before 34 weeks, the BPD status was considered unknown.	
ICD 770.7/P27.1(21)	ICD 770.7: Chronic respiratory disease arising in the perinatal period. ICD P27.1: Bronchopulmonary dysplasia originating in the perinatal period.	
Other definitions used	Oxygen / respiratory support at 28 days	
	Oxygen / respiratory support at 36 weeks or at discharge	

	Oxygen at 28 days OR oxygen at 36 weeks/discharge
	Oxygen at 28 days AND oxygen at 36 weeks/discharge
	Modified NICHD definitions: modified based on different components of the original definition

BPD, Bronchopulmonary Dysplasia; FiO_2, Fraction of Inspired Oxygen; PaO_2, Partial Pressure Arterial Oxygen; Hg, Mercury; NICHD, National Institute of Child Health and Human Development ;PMA, Post-Menstrual Age; ICD, International Classification of Diseases; NCPAP, Nasal Continuous Positive Airway Pressure;

Table 2: Characteristics of studies included in the review

Characteristic	Category	BPD not defined (n=192) n (%)	BPD defined (n=628) n (%)	P
Continent of study	Europe	73 (22)	253 (78)	0.44
	North America	76 (26)	217 (74)	
	Asia	26 (19)	108 (81)	
	Oceania	8 (22)	28 (78)	
	Transcontinental	4 (25)	12 (75)	
	South America	3 (25)	9 (75)	
	Africa	2 (67)	1 (33)	
Study sites	Multicenter	74 (24)	232 (76)	0.73
	Single	118 (23)	396 (77)	
Year of publication	2010	26 (24)	82 (76)	0.57
	2011	34 (27)	92 (73)	
	2012	25 (18)	115 (82)	
	2013	35 (25)	104 (75)	
	2014	35 (24)	108 (76)	
	2015	37 (23)	127 (77)	
Type of study*	Retrospective cohort	92 (24)	290 (76)	<0.01
	Prospective cohort	38 (23)	129 (77)	
	Randomized controlled trial/Clinical trial	40 (30)	91 (70)	
	Case-control	13 (14)	83 (86)	
	Cross-sectional	2 (10)	18 (90)	
	Survey/questionnaire	7 (54)	6 (46)	
	Case series (including before-after design)	0 (0)	11 (100)	
Primary outcome BPD in report	Yes	73 (17)	348 (83)	<0.01
	No	119 (30)	280 (70)	

*One study had a mixed design.
BPD, Bronchopulmonary dysplasia

Table 3: Characteristics of studies that defined BPD (n=628)

Characteristic	Type	Frequency	Percent
Definition used	Oxygen at 36 weeks PMA	284	45.2
	NICHD criteria	188	29.9
	Oxygen at 28 days	53	8.4
	Oxygen/respiratory support at 36 weeks PMA	37	5.9
	Oxygen at 36 weeks PMA and/or oxygen at 28 days	22	3.5
	Modified NICHD	20	3.2
	Other	8	1.3
	Vermont Oxford Network definition	7	1.1
	Combination of definition	4	0.6
	ICD code 770.7	3	0.5
	Oxygen/respiratory support at 28 days	2	0.3
Incorporation of physiological test	No	588	93.6
	Yes	37	5.9
	Partly	3	0.5
Accounting of death before definition criteria met	No	596	94.9
	Yes	32	5.1
Severity of BPD categorized	No	440	70.1
	Yes	188	29.9

BPD, Bronchopulmonary Dysplasia; NICHD, National Institute of Child Health and Human Development; PMA, Post-Menstrual Age; ICD, International Classification of Diseases

Table 4: Studies comparing different definitions of BPD incidences

Author	Population	Definition	Incidence
Palta 1998(22)	Neonates ≤1500g (n=272)	Tooley(7)	37.9%
		Shennan(8)	23.0%
Gregoire 1998(23)	24-28 weeks gestation who survived to discharge and were followed (n=217)	Tooley(7)	65%
		Shennan(8)	43%
Bancalari 2003(24)	Alive at 28 days, 500 – 1000g; GA 23-32 weeks (n=1266)	Oxygen during all of first 28 days	5.9%
		On oxygen at 28 days	57.2%
		On oxygen for ≥ 28 days	47.1%
		Shennan(8)	25%
		NICHD(12)	22.8%
Sahni 2005(25)	For neonates <1251g BW (27.3 ± 2.3 weeks GA) (n=230 studied at 28 days, n=237 studied at 36 weeks PMA)	Tooley(7)	21.1%
		Shennan(8)	7.4%
		Mild BPD(12)	13.5%
		Moderate BPD(12)	4.8%
		Severe BPD(12)	2.6%
Ehrenkranz 2005(14)	GA: <32 weeks and BW <1 kg (n=4866; 3848 had follow up data)	Tooley(7)	77%
		Tooley(7) + x-ray changes	59%
		Shennan(8)	44%
		Shennan(8) + x-ray changes	39%
		NICHD(12)	76%; Mild (30%), Moderate (30%), Severe (16%)
Bancalari 2006(13)	GA: 23-30 weeks, alive at 36 weeks PMA, (n=441)	On oxygen for all first 28 days	10%
		Tooley(7)/Bancalari(9)	55%
		On oxygen for ≥ 28 days during stay	50%
		NICHD(12)	20%
Shima 2013(26)	Neonates <32 weeks GA, <1550g (n=306)	Tooley(7)	42%
		NICHD(12) – moderate and severe	17%

Parad 2015(27)	GA: 23-28 weeks and BW <1335g (n= 76) – derivation cohort	Bancalari(9)	84%
		Shennan(8)	59%
	GA: 23-28 weeks and BW <1459g (n= 227) – validation cohort	Bancalari(9)	84%
		Shennan(8)	63%
Van Rossem 2015(19)	<32 weeks gestation who needed respiratory support between 25 and 32 days of postnatal age (n=170)	Shennan(8) ascertained from national registry (PRN)	55%
		BPD according to algorithm VON(20)	31% (21% missing information)
		BPD according to NICHD(12)	55%; Mild BPD: 17% Moderate BPD: 16% Severe BPD: 22%
Poindexter 2015(15)	Infants born between $23^{0/7}$ and $28^{6/7}$ weeks (n=765)	Shennan(8)	BPD: 41%; Unclassified: 11%
		NICHD(12)	BPD: 59% (Mild-20%, Moderate-12%, Severe- 28%); Unclassified: 2%
		Oxygen test added to NICHD(12) criteria	BPD: 32%; Unclassified: 16%
		Modified Shennan et al(8) (no BPD if discharged home before 36 weeks in room air)	BPD: 41%; Unclassified: 11%
		Modified NICHD(12) (without the requirement for at least 28 days of supplemental oxygen)	BPD: 42% (moderate: 12%; severe: 30%); Unclassified: 2%

BPD, Bronchopulmonary Dysplasia; BW, Birth Weight; GA, Gestational Age, PMA, Post-Menstrual Age; NICHD, National Institute of Child Health and Human Development; PRN, National Perinatal Registry; VON, Vermont Oxford Network

Table 5: Studies comparing different definitions of BPD and their correlation to long-term adverse outcomes

Author, Follow up age, Study Population	Definition	Long-Term Outcome Measure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Other statistics
Palta 1998(22), 5 years of age, N=272	Tooley(7)	Diagnosis of asthma	52	66	29	83	AOR 1.3; 95% CI 0.6-2.8
	Shennan(8)		43	82	40	84	AOR 2.7; 95% CI 1.3-5.7
	Tooley(7)	Respiratory hospitalization	58	68	37	83	AOR 2.8; 95% CI 1.4-5.8
	Shennan(8)		38	82	40	80	AOR 3.6; 95% CI 1.7-7.6
Gregoire 1998(23),18.5 months of age, N=217	Tooley(7)	Hospitalization due to respiratory cause	69	37	33	72	
	Shennan(8)		53	62	39	74	
	Tooley(7)	Developmental quotient < 82	72	37	20	86	
	Shennan(8)		58	60	24	86	
	Tooley(7)	Severe cerebral palsy	69	36	16	38	
	Shennan(8)		50	58	17	87	
Davis 2002(28), 18 months of age, N=809	Tooley(7)	Pulmonary outcome*	67	54	62	58	Accuracy: 61%
		Neurosensory outcome**	67	47	39	74	Accuracy: 54%
	Shennan(8)	Pulmonary outcome*	46	82	75	57	Accuracy: 63%
		Neurosensory outcome**	45	72	45	72	Accuracy: 63%
Ehrenkranz 2005(14), 18-22 months of age, N= 3848	Tooley(7)	Use of diuretics or bronchodilators	82	26	38	73	
	Tooley(7) + x-ray changes		68	44	40	72	
	Shennan(8)		54	62	44	71	
	Shennan(8) + x-ray changes		49	67	45	71	
	NICHD(12)		82	26	38	73	
	Tooley(7)	Rehospitalization due	82	25	32	76	

	Tooley(7) + x-ray changes	to pulmonary causes	67	43	34	75	
	Shennan(8)		52	60	36	74	
	Shennan(8) + x-ray changes		47	65	37	74	
	NICHD(12)		82	25	32	76	
Parad 2015(27), 24 months corrected age, N=76;N=227	Bancalari(9)	Respiratory hospital admission	NC	NC	NC	NC	AOR 3.89; 95% CI 0.45-33.6; AUC 0.55
	Shennan(8)		NC	NC	NC	NC	AOR 1.58; 95% CI 0.5-5.0; AUC 0.55
	Bancalari(9)	Any cough, wheeze, and/or use of respiratory medications	NC	NC	NC	NC	AOR 0.94; 95% CI 0.38-2.32; AUC 0.5
	Shennan(8)		NC	NC	NC	NC	AOR 1.41; 95% CI 0.69-2.9; AUC 0.54

BPD, Bronchopulmonary Dysplasia; GA, Gestational Age, PMA, Post-Menstrual Age; BW, Birth weight; OR, Odds Ratio; NICHD, National Institute of Child Health and Human Development; VON, Vermont Oxford Network; PPV, Positive Predictive Value; NPV, Negative Predictive Value; AOR, Adjusted Odds Ratio; NC, Not calculable; AUC, Area Under the Curve

*Abnormal pulmonary outcome= death from any cause; need for oxygen therapy or ventilation after discharge home; need for respiratory medication (including inhaled corticosteroids, systemic corticosteroids, and bronchodilators) for a total of more than 2 months; and readmission to hospital because of respiratory illness

** Abnormal neurosensory outcome = death from any cause; cerebral palsy; cognitive delay; hearing loss requiring amplification; and bilateral blindness

Figure 1: Flow chart of Bronchopulmonary Dysplasia (BPD) study selection